ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Prateek Sharma, MD

Adverse Events Associated With Proton Pump Inhibitors: Fact vs Fiction

Paul Moayyedi, MB ChB, PhD, MPH
Assistant Dean of Research
Audrey Campbell Chair of Ulcerative Colitis Research
McMaster University
Hamilton, Ontario, Canada

G&H What is known about the safety of proton pump inhibitors?

PM Historically, proton pump inhibitors (PPIs) have been regarded as highly safe. For any disease area where PPIs are used, when looking at the randomized trials and the huge amount of randomized trial data, most of the data being short-term (6 months to a year), the bottom line is that there are few increased adverse events seen in the PPI group compared with placebo in the relatively short-term studies. Some studies have shown a slight increase in headache and diarrhea, although with little difference between placebo and PPI, and for many studies, there was absolutely no difference in any of the short-term adverse events. However, concern was raised about long-term adverse events in 2004, when Laheij and colleagues released a paper in the *Journal of the American Medical Association* on the association between pneumonia and patients taking PPIs. Since then, there have been numerous papers evaluating the safety of PPIs.

G&H What are the concerns raised about PPI use?

PM The concerns can be anything from interacting with oncology treatment for pancreatic cancer to all-cause mortality. Among other common concerns are pneumonia (as I mentioned), increased risk of fracture, certain types of heart disease, interference with the effectiveness of the antiplatelet drug clopidogrel, chronic renal disease, heart disease in general, stroke, and dementia. Looking at all-cause mortality, it has been reported that people die more often on PPIs than when they are not taking PPIs, generally. Other concerns are chronic obstructive pulmonary disease and diabetes.

G&H Why have studies on the potential risks of PPIs shown conflicting results?

PM The studies that do not control for confounders or other factors show a positive association and then report it as a harmful effect of PPIs. The better designed the study is, usually the less of an effect is noted. For these studies, which are epidemiologic studies looking for associations, a better designed study can come in many forms; one is to carefully think about what the data mean. Modern epidemiology study started in the 1950s in the United Kingdom. Among the epidemiologists of that time were Sir Richard Doll and Sir Austin Bradford Hill who famously coauthored a paper on the association of cigarette smoking and lung cancer. An important aspect of their research is that the authors did not stop after they found the association; they realized there are other reasons for this apparent association. They continued performing various differently designed studies to prove or disprove their original finding. It was not until the 1960s when the data on the relationship became indisputable.

From that research came Hill's criteria for causation, or the 9 principles helpful for identifying evidence of a causal relationship, of which dose response and a temporal effect are very important. If there is a modest association, this is usually due to residual confounding, whereas

if one adjusted for all known confounders and the odds ratios are still above 2, it is likely that the association is causal. Although an important confounding factor that is unknown could have been missed, the chances of this are modest. If the odds ratio is 1.2, and often papers on associations with PPIs are of that magnitude, then the absolute effect is actually very small and is probably due to residual confounding. Unfortunately, because of their newsworthy potential, papers with weak associations are frequently published and highly cited, but they lack critical interpretation of the data and well-designed follow-up studies needed to support an association.

We cannot know if any of the adverse events are fact.

Another reason for conflicting results is in the study design. Propensity matching that is well done is the nearest one can get to a randomized trial. Generally, studies that use propensity matching as a way of trying to make the groups as balanced as possible tend to show modest results. In contrast, looking at the numbers without adjusting for many confounding factors, the odds ratio can appear quite a bit bigger.

G&H Which adverse events associated with PPI use are fact, and which are fiction?

PM We cannot know if any of the adverse events are fact. The one that is most likely to be true is that PPI use may increase a person's risk of infectious diarrhea. The reason I say this is because it has true biologic plausibility. When these drugs were developed, one of the biggest concerns with them was their effect on acid. Acid protects the gut from ingesting bacteria that could be harmful. Physiologically, the reason many animals have a stomach is primarily to clean food before it enters the small bowel. It makes sense that if patients have little to no acid, the more at risk they are for infection with *Salmonella* or *Campylobacter.* One of the first studies to show this association was done by Neal and colleagues. These studies were published in the 1990s when the databases and statistical sophistication that exist now were not available and by modern standards are not as well done; however, the odds ratio is still high.

In the randomized trial my colleagues and I conducted in which we randomized 17,598 patients with stable cardiovascular disease to a PPI or placebo and followed them for up to 3 years, the only positive association we showed was with infectious diarrhea. With every other adverse event we looked at (eg, fracture, pneumonia, heart disease, all-cause mortality), the odds ratio was roughly 1 with pretty narrow confidence intervals. I think we can be pretty confident that PPI therapy either has no effect, or if it does, it is very small and certainly smaller than what the papers were initially saying. Obviously, my bias is PPIs have no effect.

G&H How significant is the association between PPI use and *Clostridioides difficile* infection?

PM We could not answer this in our randomized trial, as there were so few events. The odds ratio in the trial, although not statistically significant, was over 2. Because *C difficile* infection in the community is so rare, the number needed to treat with PPIs to have 1 infection that would not have occurred otherwise is about 5000, and a risk of 1 in 5000 is one most people would be willing to take. In the community, the infection is nearly always related to antibiotic use, which alters a person's gut bacteria and allows growth of endogenous *C difficile,* rather than to ingestion of the bacteria.

This association may be different in the hospital setting, and PPIs are more likely to be relevant in this setting. It is more likely for a patient to become infected from a doctor or a nurse who has treated another patient with *C difficile* infection. Perhaps having less acid in one's stomach may facilitate the transmission, although the bacteria in a hospital would likely be in a spore form, which is acid-resistant. So, it is not entirely clear whether there is a significant association with PPI use; however, I cannot dismiss it as readily in the hospital as I can in the community because the risks there are higher (eg, patients are vulnerable, *C difficile* is more prevalent). PPI use could be an issue.

G&H Is there a risk of cardiovascular disease with use of PPIs?

PM The answer is pretty confidently no. This is because of the results of the COMPASS study conducted by my cardiology colleagues at McMaster. The study enrolled 27,395 participants with stable atherosclerotic vascular disease and evaluated whether rivaroxaban with or without aspirin could reduce cardiovascular events in people at high risk of having cardiovascular events. I became involved because the study was using an anticoagulant and maybe a PPI to stop gastrointestinal (GI) bleeding associated with the anticoagulants. Participants who were not on a PPI already, about 17,500, were randomized to a PPI or placebo to see whether bleeding events could be

prevented. However, we realized that we could also look at adverse events to determine whether PPIs cause adverse events, and I was grateful to my cardiology colleagues for adding this in and extending the trial another year to look for GI bleeding and other adverse events. At every 6-month follow-up over 3 years, they asked each patient about renal disease, dementia, fractures, and other adverse events. It is important to emphasize that these data were less well characterized than for heart disease, as this was a secondary endpoint of the trial. Over the course of the study, a lot of adverse events were accurately recorded, and there was no difference at all between the PPI group and the placebo group. We can be pretty confident that PPI use does not cause heart disease.

G&H What have recent data shown about the risk of cancer with long-term use of PPIs?

PM There are data that suggest long-term PPI use might be associated with pancreatic cancer and other cancers. These data tend to vary by specialty. There are some data on risk of stomach cancer. Unpicking this risk is tricky because a patient with stomach pain treated with a PPI may initially have had stomach cancer that was not diagnosed until 2 years later. Some studies have focused on *Helicobacter pylori*–negative stomach cancer. However, there is a theoretical reason why PPIs could cause stomach cancer in a patient infected with *H pylori.* If a patient is *H pylori*-positive and given a PPI, then risk status moves from *H pylori* being just at the bottom end of the stomach, the antrum, where the risk of stomach cancer is very low, to one where *H pylori* can spread all over the stomach, where the risk of stomach cancer increases in the long term. Again, I do not think the data are strong enough to say that is true. It is a theoretical risk.

When discussing increased cancer risk, the definition of long term is important. In the community, patients may be on PPIs for a long time before undergoing an endoscopy, and stomach cancer can be present for quite a while before it becomes clinically apparent. A study period of 6 months, even 2 years, is not enough to determine cancer risk, and often, although there are exceptions, studies examining this risk do not provide that type of window.

A study period of 6 months, even 2 years, is not enough to determine cancer risk, and often, although there are exceptions, studies examining this risk do not provide that type of window.

G&H Which concerns would you discuss with patients prior to PPI use?

PM For patients who are worried about taking a PPI, I tell them about the randomized data and explain why things can appear associated that are not. I also say that sicker people, meaning those who have comorbid conditions, on average are more likely to be on PPIs, making it easy to find diseases for PPI use to be associated with. It does not mean that one causes the other. Over the years, in my practice, the only thing I have counseled patients on is the risk of GI infection, and that the risk of infection is very small in Canada or the United Kingdom, for example. However, the risk is relevant to a patient going to a high-risk country like India, where the likelihood of acquiring a GI infection is higher. Patients can either be extra careful or refrain from taking their PPI during that holiday.

G&H What are the best practices for PPI use, patient education, and current preventive measures?

PM There is extensive evidence on the effectiveness of PPIs from randomized trials for esophagitis for which the number needed to treat is almost 1, for reflux disease in general, dyspepsia, for management of indigestion and stomach pain, for prevention of GI bleeding when taking nonsteroidal anti-inflammatory drugs (NSAIDs) in those at high risk (eg, for patients who have had a bleeding ulcer in the past and must take NSAIDs), and peptic ulcer disease, after treatment of *H pylori* infection.

Using a PPI is important for patients with Barrett esophagus, where the lining of the esophagus changes and usually causes heartburn. However, even patients without heartburn should take a PPI because of the high risk of Barrett esophagus, which can lead to esophageal adenocarcinoma, and PPIs reduce that risk. In another randomized trial (AspECT), my colleagues and I found that all-cause mortality was reduced in PPI users, particularly with a combination of a PPI plus aspirin, compared with patients taking neither. The bottom line is even if PPI use does rarely cause some of the adverse effects I mentioned, overall, the benefits outweigh the risks, and in the case of patients with Barrett esophagus, taking a PPI can help them live longer.

G&H How can future research on PPIs be improved?

PM Future trials could go into much greater detail on secondary biomarkers. For renal disease, my colleagues and I recently conducted a trial in which we checked patients' creatinine clearance before and after finishing a PPI trial. We had roughly 4000 patients in each group and noted a very minor difference in the levels but not much. For every patient, very detailed information was obtained on their renal function and how it is deteriorating. Everyone deteriorates with age, but the rate of degeneration is not that much different in PPI users. We also administered cognitive tests over the phone and asked about dementia. However, what about having patients complete other cognitive tests? Is cognitive decline different between the PPI users and the placebo users? Again, there was no difference in our study. However, evaluation of these objective secondary markers of possible harm is an area where more research could be done. Other than that, I think our randomized trial has disproved most of the significant associations. Gastroenterologists should stop listening to sensational observational, sometimes poorly conducted, research.

Gastroenterologists should stop listening to sensational observational, sometimes poorly conducted, research.

Disclosures

Dr Moayyedi has no relevant conflicts of interest to disclose.

Suggested Reading

Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017;377(14):1319-1330.

Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. *Can Fam Physician.* 2017;63(5):354-364.

Jankowski JAZ, de Caestecker J, Love SB, et al; AspECT Trial Team. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. *Lancet.* 2018;392(10145):400-408.

Laheij RJF, Sturkenboom MCJM, Hassing RJ, Dieleman J, Stricker BHC, Jansen JBMJ. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA.* 2004;292(16):1955-1960.

Leontiadis GI, Veldhuyzen Van Zanten S, Hookey L, Armstrong D, Jones N, Moayyedi P. Canadian Association of Gastroenterology statement on the putative link between proton pump inhibitor treatment and gastric cancer after *Helicobacter pylori* eradication. *J Can Assoc Gastroenterol.* 2018;1(4):155-158.

Moayyedi P, Eikelboom JW, Bosch J, et al; COMPASS Investigators. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology.* 2019;157(3):682-691.e2.

Moayyedi P, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. *Am J Gastroenterol.* 2017;112(7):988-1013.